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Please find below and/or attached an Office communication concerning this application or proceeding.

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Continuation of Item 5: Applicants' reply has overcome the rejection of claim 29 under 35 USC 112, second paragraph; however the amendment has necessitated new grounds of rejection of claim 29 under 35 USC 103(a).

Continuation of Item 7:

Claims 1-4, 6, 8, 9, 12, 23, 25, 26, 28, 29, 40, 41 and 43 are rejected under 35 U.S.C. 103(a) as being obvious over Badylak et al (US 2003/0216811), in light of Badylak et al (Biomaterials, 1999), and in view of Penn et al (US 2004/0161412 A1). Please note the amendment to claim 29 has necessitated its inclusion in this grounds of rejection.

Badylak et al disclose submucosa tissue-derived grafts and methods of using said grafts to repair damaged or diseased tissues. Specifically, the tissue graft comprises a vertebrate intestinal submucosa tissue seeded with endothelial cells and at least one additional exogenous cell population (See Badylak et al, ¶0016). Badylak et al report their method is particularly effective in promoting vascularization at the target tissue site (See Badylak et al, ¶0022).

The endothelial cells can be any type of endothelial cell, including vascular endothelial cells (See Badylak et al, ¶0017).

The at least one additional exogenous cell population may be selected from fibroblasts, smooth muscle cells, skeletal muscle cells, cardiac muscle cells, multi-potential progenitor cells, pericytes, osteogenic cells, or any other suitable cell type (See Badylak et al, ¶0018). The at least one additional exogenous cell population may be selected based on the type of tissue to be repaired, i.e. the at least one additional exogenous cell population may be selected to be a tissue-specific cell type; cardiac muscle cells are specifically disclosed for instances where cardiac tissue is to be repaired (See Badylak et al, ¶0019).

Badylak et al disclose the intestinal submucosa may be in an injectable fluidized or gel form (See Badylak et al, ¶0005 & 0033).

In use, the submucosa-tissue derived graft is seeded with the population of endothelial cells and the at least one additional exogenous cell population *in vitro*; cultured *in vitro* for a time sufficient to induce formation of vessels or vessel-like structures; and then injected into a vertebrate at the site in need of repair (See Badylak et al, e.g., ¶0049).

The method of Badylak et al is comparable to the method of the instant claims as follows:

The intestinal submucosa is considered to appropriately read on a matrix material which may form an organ construct. Intestinal submucosa comprises collagen type I (See Badylak et al, Biomaterials, Pg. 2257, 2nd full paragraph); collagen is a naturally occurring polymer, thus the submucosa comprises a polymer.

In the injectable form the intestinal submucosa is considered to appropriately read on an injectable polymer matrix that comprises collagen type I (as recited in claims 1, 8 and 9); the injectable form further reads on the matrix material of claims 23 and 26 and may be considered a hydrogel (claim 25).

For the purposes of this rejection either of the vascular endothelial cells or the at least one additional exogenous cell population may be considered the first or the second cell population, as both cell populations are intended to be assimilated into the target tissue region. Thus, the step of co-culturing the vascular endothelial cells and the at least one additional exogenous cell population is comparable to the claimed step of "selecting a second population of cells to be assimilated at a target tissue region upon implantation" (claim 1) as well as the step of "culturing at least a second population of cells on a matrix material to produce an organ construct" (claim 23).

Finally, the step of injecting the cell-seeded tissue graft into a target tissue region is considered to read on the claimed step of "injecting the first population of cells and the second population of cells and the polymer matrix into the target tissue region" (claim 1) as well as the step of "implanting the organ

construct and the first population of cells *in vivo* at a target site to replace or augment organ function" (claim 23). Both the endothelial cells and the at least one additional exogenous cell population assimilate into the target tissue region, thereby augmenting organ function (claim 29).

The method of Badylak et al differs from the claimed method in that Badylak et al does not disclose a step of transiently transfecting the first population of cells (which may be either cell population) with a plasmid encoding an angiogenesis modulating agent, specifically VEGF, so that, upon injection the first population of cells will express the angiogenesis modulating agent (VEGF).

However, at the time the invention was made it was well known in the art that cells intended for transplantation for organ augmentation may be genetically engineered to express one or more growth factors which will promote cell survival and angiogenesis; this technique is known as cell-based gene therapy (See, e.g. Penn et al ¶0009 & 0067-0072).

Penn et al teach implantation of skeletal myoblasts which have been transfected with VEGF into ischemic myocardium in order to restore function to the ischemic cardiac tissue (See Penn et al ¶ 0067-0070). The transfection may be achieved by vector-based plasmid DNA transfection (See Penn et al, ¶0092 & ¶0100-0102)). Furthermore, Penn et al state that the myoblasts cells which transiently express VEGF are useful to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, ¶0020 & ¶0044-0045). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization, while minimizing systemic effects and hemangioma formation (See Penn et al, ¶0004 & 0099-0102).

With regards to the length of time the VEGF is produced, Penn et al teach that the duration of the transient expression is a result effective variable that would be routinely optimized by one of ordinary skill in the art (See Penn et al, pg. 8, paragraphs 0099-0102). Penn et al teach that the cells can be

transiently transfected so as to express a therapeutic amount of VEGF; Penn et al further teaches that it is well within the scope of one skilled in the art to determine the appropriate therapeutic amount on an individual basis, as factors such as size, age, sex, presence of other drugs, and concentration of the active drug, all effect the optimal duration of expression. Therefore, the duration of the transient expression of VEGF would have been routinely optimized by one of ordinary skill in the art at the time the invention was made, especially with lack of evidence supporting the claimed time period is critical (relevant to claim 2).

It is submitted that, based on the teachings of Badylak et al and Penn et al, one of ordinary skill in the art would have found it *prima facie* obvious to utilize the transiently transfected myoblasts of Penn et al as the 'at least one additional exogenous cell population' in the graft of Badylak et al, and to then apply the graft, containing vascular endothelial cells and transiently transfected myoblasts, to ischemic myocardium in order to induce growth and development of blood vessels in the ischemic tissue, thereby improving cardiac function. One would have been motivated to combine the prior art elements in order to produce an improved treatment option for ischemic myocardium, as prior art methods had varying degrees of success. Particular motivation is based on the fact that treatment for myocardial ischemia involves angiogenesis and vasculogenesis of the ischemic tissue (See Penn et al, ¶0004); Badylak et al state their tissue graft is particularly effective at inducing vascularization (See Badylak et al, ¶0022); Penn et al state the myoblasts form new cardiac muscle tissue (See Penn et al, ¶0070), and the VEGF is an angiogenic promoting agent that increases vascular density (See Penn et al, ¶0044).

One would have had a reasonable expectation of successfully employing the transiently transfected myoblasts of Penn et al as the 'at least one additional exogenous cell type' because Badylak et al disclose skeletal muscle cells as one type of cell which may be provided as the tissue specific at least

one additional exogenous population of cells (See Badylak et al, ¶0018-0019). Myoblasts are progenitor muscle cells, thus skeletal myoblasts may be considered a species of skeletal muscle cell.

Thus it is submitted that it would have been *prima facie* obvious to one having ordinary skill in the art to modify the method of Badylak et al so as to utilize the myoblasts of Penn et al, which are transiently transfected with a plasmid encoding VEGF, as the 'at least one additional exogenous cell population' in the tissue graft of Badylak et al. In this manner the transiently transfected myoblasts may be considered 'the first cell population', and the vascular endothelial cells may be considered 'the second cell population. The graft may be injected into ischemic myocardium where the myoblasts will necessarily express the VEGF thereby supporting cell survival and assimilation and differentiation of both the myoblasts and endothelial cells into the myocardial tissue to improve cardiac function. Thus the modified method of Badylak et al reads on the method of instant claims 1, 2, 12, 23, 29 and 41. Please note that myoblasts (the first cell population) are also considered to read on undifferentiated cells (claim 3).

Alternatively, it would have been within the purview of one skilled in the art to transiently transfect the *vascular endothelial cells* with a plasmid encoding VEGF (per the method of Penn et al) and to seed the transiently transfected vascular endothelial cells with normal myoblasts onto the injectable submucosa matrix of Badylak et al. It is not critical which cell type expresses the VEGF, but rather only that at least one cell type which is provided to the target tissue is capable of expressing the VEGF in order to increase the concentration of VEGF at the target site. Penn et al disclose that the transfection method is applicable to any cell type (See Penn et al, ¶0069), thus one would have had a reasonable expectation of successfully transiently transfecting the vascular endothelial cells as opposed to the myoblasts. In this manner, the transiently transfected *vascular endothelial cells* may be considered 'the first cell population',

and the myoblasts may be considered 'the second cell population.' The graft may be injected into ischemic myocardium where the vascular endothelial cells will necessarily express the VEGF thereby supporting cell survival and assimilation and differentiation of both the myoblasts and endothelial cells into the myocardial tissue to improve cardiac function. Thus the modified method of Badylak et al reads on the method of instant claims 1, 2, 4, 6, 23, 29, 40 and 43.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 1-4, 6, 8, 9, 10, 12, 23, 25, 26, 28, 29, 33-37, 40, 41 and 43 stand rejected under 35 U.S.C. 103(a) as being obvious over Badylak et al (US 2003/0216811), in light of Badylak et al (Biomaterials, 1999), and in view of Penn et al (US 2004/0161412 A1), and further in view of Stewart et al (US 2006/0251630 A1). Please note the amendment to claim 29 has necessitated its inclusion in this grounds of rejection.

The teachings of Badylak et al and Penn et al are set forth in detail above. Briefly, Badylak et al disclose a method for repairing damaged or diseased tissue comprising:

providing a fluidized intestinal submucosa material as a matrix;

co-culturing vascular endothelial cells and at least one additional, tissue-specific exogenous cell population on the intestinal submucosa matrix to form a tissue graft; and

injecting the cell-seeded tissue graft to a target tissue region in need of repair.

Upon implantation the cell populations assimilate into the tissue site, and promote vascularization at the implantation site.

Badylak et al differs from the method of the instant claims in that they do not teach transiently transfecting either of the cell populations with a plasmid encoding an angiogenesis modulating agent, specifically VEGF.

Penn et al is relied upon for their disclosure that cell-based gene therapy, which involves transplantation of a cell type which has been transfected to express a therapeutic gene product, such as a growth factor, was an accepted technique in the art. Penn et al particularly disclose a method for augmenting cardiac function in ischemic myocardium by delivering myoblasts which have been transiently transfected with a plasmid encoding VEGF. Penn et al disclose the myoblasts assimilate into the cardiac tissue to restore function, and the VEGF increases vascular density, which is critical for restoring function in ischemic tissues.

Taken together, the references are held to render obvious a method wherein the transfected myoblasts of Penn et al are utilized as the 'at least one additional exogenous cell type' in the tissue graft of Badylak et al, and the thus modified tissue graft is injected into ischemic myocardium to increase vascularization and restore cardiac function.

The combination of references still differs from current claims 10 and 33 in that neither Badylak et al nor Penn et al teach or suggest encapsulating the transfected first cell population, and specifically do not teach encapsulation in alginate-PLL (poly(L-lysine)) microspheres (claims 34-37).

However, at the time the invention was made it was routine in the art to encapsulate cells so as to physically protect the transplanted cells from the recipients immune system, in this manner cells which secrete therapeutic agents, such as growth factors, hormones, etc, may be transplanted to a recipient to provide the therapeutic agent, but are protected from immune rejection (See Stewart et al, ¶0003-0006).

In the method suggested by the art the transfected cell population is provided for the production of growth factor. As taught by Stewart et al, any transplanted cell may be subject to immune rejection, thus, in order to protect the genetically engineered cells to ensure that they survive to express the VEGF, it is submitted that it would have been *prima facie* obvious to one having ordinary skill in the art to encapsulate the genetically engineered first cell population, and provide this encapsulated first cell population along with the cell-based tissue construct of Badylak et al to the target tissue site. Stewart et al disclose various microcapsules, including alginate-poly(L-lysine) microcapsules (please note microcapsules and microspheres are synonymous in this context) (See Stewart et al, ¶0010) (claims 10, 33-37).

One would have had a reasonable expectation of successfully encapsulating the genetically engineered cell population in microspheres, such as alginate-poly(L-lysine) microspheres, because methods of such encapsulation were well known in the art, and are specifically disclosed by Stewart et al. Furthermore, Stewart et al disclose encapsulation of cells which have been genetically engineered to express VEGF (See Stewart et al, ¶0107).

Therefore, it is submitted that encapsulation of the 'first population of transfected cells', per the techniques disclosed by Stewart et al, in the method suggested by Badylak et al and Penn et al would have been *prima facie* obvious to one skilled in the art in order to ensure immune privilege and physical protection for the genetically engineered cells of the tissue graft, so as to ensure the successful production of VEGF, which is beneficial in angiogenesis.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 25, 26, 28 and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Penn et al (US 2004/0161412 A1) for the reasons

of record. Please note the amendment to claim 29 has necessitated its inclusion in this ground of rejection.

Naughton et al disclose a method for promoting blood vessel formation in tissues and organs by implanting a three-dimensional stromal tissue construct at a target site at or near the tissue or organ to promote endothelialization and angiogenesis in the tissue or organ. Naughton et al specifically disclose promoting blood vessel formation in the heart, including promoting vascularization and healing of ischemic myocardial tissue (See Naughton ¶ 0007-0008, 0028 & especially 0055-0057). The stromal tissue construct of Naughton et al is produced by:

(i) Providing a three-dimensional framework which allows cells to attach and grow in more than one layer. Materials suitable for the three-dimensional framework are disclosed at paragraphs 0032-0033 of Naughton et al, included in the listed materials are a number of polymers, such as nylon, Dacron, polystyrene, polypropylene, polyacrylates (¶0032), polyglycolic acid, collagen, and polylactic acid (¶0033). Collagen gel is also disclosed (¶0033); collagen gel is considered to read on a hydrogel0.

(ii) Selecting a stromal cell population and inoculating said stromal cell population onto the three-dimensional framework. The stromal cells may be fibroblasts, or "specific" stromal tissue may be selected, such as stromal cells derived from the heart (See Naughton et al, ¶0034). Additional cell types may be seeded along with the fibroblasts/stromal cells, such additional cell types may include endothelial cells, skeletal muscle cells and cardiac muscle cells (See Naughton et al, ¶0038).

(iii) Culturing the stromal cell population with or without additional cell populations to form the three-dimensional stromal tissue construct (See Naughton et al, ¶0041-0045).

In a specific embodiment Naughton et al disclose preparing a genetically engineered three-dimensional stromal tissue by selecting stromal cells which are engineered to express an exogenous gene product (See Naughton et al, ¶0046-0048). The exogenous gene product secreted by the genetically engineered cells may enhance cell growth and/or promote angiogenesis; VEGF is specifically disclosed

(See Naughton et al, ¶0049-0050) (relevant to claim 28). Cells that may be genetically engineered to express the exogenous gene product include the stromal cells, such as fibroblasts; Naughton et al also state additional cell types which can be genetically engineered include endothelial cells, smooth muscle cells, cardiac muscle cells, etc (See Naughton et al, ¶0048).

The stromal tissue construct of Naughton et al is then implanted at a target tissue site, such as adjacent to ischemic myocardium (See Naughton et al, ¶0055-0058). The stromal tissue construct may attach via natural adherence (i.e. the cells of the stromal tissue will assimilate into the existing tissue) and will promote formation of new blood vessels and healing within the target tissue (See Naughton et al, ¶0067-0068). Expression of the VEGF by the 'first cell population' will necessarily promote survival of both the stromal cells (second cell population) and the first cell population present within the tissue construct, as well as promote angiogenesis in the ischemic tissue.

The embodiment wherein the stromal cells and an additional cell population are co-cultured together on the three-dimensional framework, and wherein the 'additional cell population' comprises genetically engineered cells, is being relied upon for this rejection; the method of Naughton et al is comparable to the method of the instant claims as follows:

The three-dimensional framework is considered to read on a matrix material as defined by the instant claims. The three-dimensional framework may be comprised of a polymeric material, such as a woven mesh of PGA, PLA, collagen (relevant to claim 26), or of a collagen gel (relevant to claim 25).

The stromal cells are considered to read the second cell population, as defined by the claims, and the additional cells are considered to read on the first cell population, as defined by the claims.

The step of genetically engineering the additional cell type (the 'first population of cells') to express VEGF is comparable to the claimed step of "transiently transfecting a first population of cells

with a plasmid encoding an angiogenesis modulating agent." VEGF as the angiogenesis modulating agent is relevant to claim 28.

The step of actively culturing the stromal cell population (the 'second population of cells') and the genetically engineered additional cell population (the 'transfected first population of cells') on the three-dimensional framework is considered to read on the claimed step of "culturing at least a second population of cells on a matrix material to produce an organ construct."

Finally, the step of implanting the stromal tissue comprising the stromal cells (the 'second cell population') and the genetically engineered additional cell population (the 'transfected first cell population') adjacent to ischemic myocardial tissue is considered to read on the claimed step of "implanting the organ construct and the first population of cells *in vivo* at a target site to replace or augment organ function, such that the first population of cells express the angiogenesis modulating agent and assimilate into a tissue layer" (relevant to claim 29). Expression of the VEGF by the 'first cell population' will necessarily promote survival of both the stromal cells (second cell population) and the first cell population present within the tissue construct, as well as promote angiogenesis in the ischemic tissue, thus the method of Naughton et al is considered to effectively "induce the second population of cells to assimilate and differentiate at the target site."

The method of Naughton et al differs from the instant claims with regards to the step of *transiently* transfecting the first population of cells *with a plasmid* encoding an angiogenesis modulating agent. Naughton et al uses viral transfection methods to insert the desired gene sequence into the cell DNA under control of a promoter (See Naughton et al, ¶0052-0054); Naughton et al further does not teach transient transfection.

However, at the time the invention was made Penn et al taught a method for transiently transfecting a population of skeletal myoblasts with a VEGF expression vector by plasmid DNA transfection (See Penn et al, ¶0092 & ¶0100-0102)).

Because both Naughton et al and Penn et al disclose methods for successfully genetically engineering cells to express a target gene product (specifically VEGF), it would have been obvious to one skilled in the art to substitute one method (plasmid DNA transfection, as taught by Penn et al) for the other (viral transfection, as taught by Naughton) to achieve the predictable result of transfecting the cell so that it expresses the target gene produce (VEGF). Substitution of one method step for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395.

Furthermore, Penn et al state that the myoblasts cells which transiently express VEGF are useful to stimulate cell differentiation and regenerate ischemia damaged tissue (See Penn et al, ¶0020 & ¶0044-0045). Penn et al teach that local and transient expression of VEGF is sufficient to induce neovascularization, while minimizing systemic effects and hemangioma formation (See Penn et al, ¶0004). Because local and transient expression of the VEGF in ischemic myocardial tissue can achieve the same benefits of stimulating cell differentiation and tissue regeneration without the negative consequences of constitutive expression of VEGF (hemangioma formation) it is submitted that one would have been motivated to transiently transfect the cells by the method of Penn et al.

Because Naughton et al disclose an embodiment wherein the stromal tissue construct of is implanted adjacent to ischemic myocardium for the purpose of restoring or improving cardiac function by inducing angiogenesis at the ischemic region (See Naughton et al, ¶0055-0058), one having ordinary skill in the art would have been motivated to apply the technique of Penn et al, involving transiently

transfecting cells to transiently express VEGF to the cells contained within the stromal construct of Naughton et al for the purpose of reducing the likelihood of hemangioma formation while still stimulating angiogenesis. One would have had a reasonable expectation of successfully transiently transfecting the additional cell population (the endothelial and/or cardiac muscle cells) of Naughton et al by the techniques of Penn et al based on the success shown by and detailed protocols provided by Penn et al in their disclosure.

Thus it is submitted that it would have been *prima facie* obvious to one having ordinary skill in the art to modify the method of Naughton et al so as to transiently transfecting the 'first cell population' with a plasmid encoding VEGF so that the cells transiently express the VEGF; with this modification, the method of Naughton et al reads on the method of instant claims 23, 26 and 28.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 25, 26, 28, 29, 40 and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Penn et al (US 2004/0161412 A1). Please note the amendment to claim 29 has necessitated its inclusion in this ground of rejection.

The teachings of Naughton et al and Penn et al are set forth in detail above. Briefly, Naughton et al disclose a method for augmenting organ function, specifically improving cardiac function of ischemic myocardial tissue, comprising:

transfecting a first population of cells to express angiogenesis modulating agent VEGF;

co-culturing the transfected first population of cells with a second population of stromal cells on a three-dimensional matrix to form an organ construct; and

implanting the organ construct adjacent to ischemic myocardial tissue.

Upon implantation both cell populations assimilate into the tissue site, thereby improving cardiac function and promoting angiogenesis. The transfected first population of cells will necessarily express the VEGF, which will aid in survival of the cells of the transplanted organ construct, as well as improve angiogenesis at the target tissue site.

Naughton et al differs from the method of the instant claims in that they do not teach transiently transfecting the first cell population with a plasmid encoding VEGF. However, it has been shown that it would have been *prima facie* obvious to modify the method of Naughton et al to utilize transient transfection by plasmid based on the teachings of Penn et al, who teach that transient transfection of VEGF is desirable in treatment of ischemic myocardium because it is sufficient to induce angiogenesis, but does not cause hemangioma formation.

The method of Naughton et al differs from current claims 40 and 41 in that Naughton et al does not disclose vascular endothelial cells (claim 40) or myoblasts (claim 41) as the additional cell population (the 'first cell population') which may be genetically engineered to express VEGF.

However, Naughton et al defines the additional cell population using non-limiting language (See Naughton et al, ¶0038). Naughton et al does disclose endothelial cells (generically) and both skeletal and cardiac muscle cells (Naughton et al, ¶0038).

With regards to vascular endothelial cells, it is first reiterated that Naughton et al does suggest endothelial cells (generically), it is submitted that it would have been *prima facie* obvious to one of ordinary skill in the art to utilize *vascular* endothelial cells within the organ construct because Naughton et al intends to promote formation of blood vessels at the target tissue site. Vascular endothelial cells present within the organ construct could readily participate in development of new blood vessels as part of angiogenesis, as blood vessels comprise vascular endothelial cells. One would have had a reasonable expectation of successfully employing vascular endothelial cells as the "transiently transfected first cell

population" which may be employed in the method of Naughton et al because Penn et al disclose a process for transiently transfecting cells using a plasmid DNA transfection (See Penn et al, ¶0092); the same transfection method may be applied to any cell type (See Penn et al, ¶0069).

With regards to myoblasts, it is reiterated that Naughton et al does suggest both skeletal and cardiac muscle tissue; myoblasts are muscle progenitor cells. Furthermore, it is submitted that Penn et al specifically disclose myoblasts as a desirable cell type for implantation at a site of ischemic myocardium for augmentation of cardiac function (See Penn et al, ¶0020 & ¶0044-0045); therefore myoblasts were recognized in the art as being utility in treating myocardial ischemia. One would have had a reasonable expectation of successfully employing myoblasts as the "transiently transfected first cell population" which may be employed in the method of Naughton et al because Penn et al specifically exemplify transient transfection of myoblasts to transiently express VEGF.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23-26, 28 and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Penn et al (US 2004/0161412 A1), and further in view of Atala (US Patent 6,479,064). Please note the amendment to claim 29 has necessitated its inclusion in this ground of rejection.

The teachings of Naughton et al and Penn et al are set forth in detail above. Briefly, Naughton et al disclose a method for augmenting organ function, specifically improving cardiac function of ischemic myocardial tissue, comprising:

transfecting a first population of cells to express angiogenesis modulating agent VEGF;

co-culturing the transfected first population of cells with a second population of stromal cells on a three-dimensional matrix to form an organ construct; and

implanting the organ construct adjacent to ischemic myocardial tissue.

Upon implantation both cell populations assimilate into the tissue site, thereby improving cardiac function and promoting angiogenesis. The transfected first population of cells will necessarily express the VEGF, which will aid in survival of the cells of the transplanted organ construct, as well as improve angiogenesis at the target tissue site.

Naughton et al differs from the method of the instant claims in that they do not teach transiently transfecting the first cell population with a plasmid encoding VEGF. However, it has been shown that it would have been *prima facie* obvious to modify the method of Naughton et al to utilize transient transfection by plasmid based on the teachings of Penn et al, who teach that transient transfection of VEGF is desirable in treatment of ischemic myocardium because it is sufficient to induce angiogenesis, but does not

The combination of references still differs from current claim 24 in that Naughton et al does not disclose use of a decellularized tissue as the three-dimensional scaffold material for formation of the stromal tissue construct.

However, it is submitted that Naughton et al use open language to define the material of the three-dimensional framework which may be used as the matrix material, Naughton et al state the only requirements for the matrix material are that it must be (a) allow cells to attach to it (or can be modified to allow cells to attach to it); and (b) allows cells to grow in more than one layer (See Naughton et al, ¶0031).

At the time the invention was made the art taught numerous matrix materials which satisfied the requirements of Naughton et al for use as the three-dimensional framework material, including

decellularized tissue. Specifically, Atala discloses decellularized tissues as suitable matrix material for formation of an artificial organ (See, Atala, ¶ 0012). Matrices used by Atala allow cells to attach and to develop into neomorphic organ augmenting units, which would be understood to comprise cells growing in more than one layer (See Atala, ¶0009-0011).

Therefore, because Naughton et al and Atala both disclose scaffold materials which are capable of supporting cell attachment and growth in more than one layer, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one matrix material (the decellularized tissue of Atala) for the other (the disclosed materials of Naughton et al) for the predictable result of successfully supporting growth of cells thereupon for formation of an engineered tissue construct which may subsequently be implanted at a target site. Substitution of one element for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 25, 26, 28, 29, 33, 36 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al (US 2003/0007954), in view of Penn et al (US 2004/0161412 A1), and further in view of Stewart et al (US 2006/0251630). Please note the amendment to claim 29 has necessitated its inclusion in this ground of rejection.

Continuation of Item 11:

1. Applicants have objected to the finality of the Office Action dated 3/30/2010, asserting that the new grounds of rejection made over Badylak et al (US 2003/0216811), in view of Badylak et al (Biomaterials, 1999), and Penn et al (US 2004/01611412) was *not* necessitated by amendment because the scope of the recited matrix material was not changed By the amendment.

The finality of the previous office action is upheld, as the amendments to the claims did significantly change (broaden) the scope of the claims. In considering the claims in their amended state the new grounds of rejection over primary reference Badylak et al was deemed necessary. Further traversal of the finality of the previous office action should be pursued by a petition according to MPEP 1002.02(c).

2. Applicants have traversed the restriction requirement withdrawing claims 7, 38, 39 and 42, asserting that there was no basis for the assertion that "the species of vascular endothelial cells and myoblasts have been constructively elected by original presentation for prosecution on the merits." Applicants argue that the original claims, and claims which were examined throughout prosecution were generic to cell types which encompassed the species of "endothelial progenitor cells."

This argument is not found persuasive. The original claims (submitted 1/28/2004) defined two populations of cells, one population being "undifferentiated cells" (claim 4), "vascular endothelial cells" (claim 5) or "myoblasts" (claims 12 and 27), and the other population of cells being "undifferentiated cells" (claim 5), "vascular endothelial cells" (claim 6) or "myoblasts" (claim 27). Endothelial progenitor cells are a species of undifferentiated cells, myoblasts are another species of undifferentiated cells. Had both myoblasts and endothelial progenitor cells been originally presented for examination, a requirement to elect a single species of undifferentiated cell type for examination on the merits would have been required; however endothelial progenitor cells was not originally presented as a species, only myoblasts, because the species of myoblast was examined, myoblasts are considered to have been *constructively*

elected by original presentation for prosecution on the merits. Though Applicants assert that endothelial progenitor cells are a type of vascular endothelial cell, it is respectfully submitted that such is not accurate, endothelial progenitor cells are not limited to *vascular* endothelial progenitor cells, yet, even if they were, mature vascular endothelial cells are considered a distinct species from vascular endothelial *progenitor* cells, for the reasons set forth in the Final Office action of 3/30/2010 (pg. 2).

3. Applicants have traversed the rejection of claims 1-4, 6, 8, 9, 12, 23, 25, 26, 28, 40-41 and 43 as being obvious over Badylak et al (2003), in light of Badylak et al (1999), and in view of Penn et al (2004) on the grounds that Badylak et al (2003) fails to define the "at least one additional cell population" which is to be included along with the endothelial cells on the submucosal tissue graft with sufficient specificity to enable one having ordinary skill in the art to appropriately select an appropriate secondary cell type, much less a secondary cell type which is transiently transfected to express an angiogenesis modulating agent or VEGF, as required by the instant claims. Applicants further traverse on the grounds that the Office Action fails to provide any "nexus" between the primary and secondary references, asserting that reliance on Penn is based on impermissible hindsight.

Applicants' arguments have been fully considered, but are not found persuasive.

First, it is respectfully submitted that though Badylak et al (2003) does broadly define the second population of cells, it would not have been undue experimentation for having ordinary skill in the art to select an appropriate secondary cell type based on the intended downstream application. Culture of animal cells was routine in the art at the time the invention was made. Cells were known, means to obtain almost any type of cell were available, and appropriate culture methods for different types of cells were within the purview of the skilled artisan. Therefore, though Badylak et al broadly reference "mesodermally derived" cells as a possibility for the 'at least one additional cell population,' based on the

state of the art and the skill of the artisan in the field, the disclosure of Badylak et al is found to be enabling for the full scope of cell types which may be included within the breadth of their disclosure.

Second, regarding Badylak et al (1999), it is respectfully submitted that Badylak et al (1999) is relied upon solely for disclosure of a fact: that intestinal submucosa contains collage type I. The lack of other relevant teachings in Badylak et al (1999) is immaterial to the grounds of rejection.

Thirdly, regarding Penn et al (2004), though Applicants have asserted there is no established 'nexus' between the primary reference Badylak et al (2003) and Penn et al (2004), it is respectfully submitted that both references are directed to cell-based implants for tissue engineering, and specifically for promoting vascularization at the implant site. Badylak et al specifically report their method is particularly effective in promoting vascularization at the target tissue site (See Badylak et al, ¶0022). Penn et al provides an embodiment for improving vascularization of ischemic myocardium by injection of transiently transfected cells (See, e.g. Penn et al ¶0009 & 0067-0072). Rationale for combining the cited references has been clearly set forth: "One would have been motivated to combine the prior art elements in order to produce an improved treatment option for ischemic myocardium, as prior art methods had varying degrees of success. Particular motivation is based on the fact that treatment for myocardial ischemia involves angiogenesis and vasculogenesis of the ischemic tissue (See Penn et al, ¶0004); Badylak et al state their tissue graft is particularly effective at inducing vascularization (See Badylak et al, ¶0022); Penn et al state the myoblasts form new cardiac muscle tissue (See Penn et al, ¶0070), and the VEGF is an angiogenic promoting agent that increases vascular density (See Penn et al, ¶0044)." Therefore, the rejection is maintained as proper.

4. Applicants have traversed the rejection of claims 1-4, 6, 8-10, 12, 23, 25, 26, 28, 33-37, 40, 41 and 43 under 35 USC 103(a) over Badylak et al (2003), in light of Badylak et al (1999), in view of Penn (2004) and further in view of Stewart et al (2006) on the grounds that the combination of teachings of

Badylak et al (2003), Badylak et al (1999) and Penn (2004) are inappropriate for the reasons set forth above, and that Stewart et al (2006) fails to remedy the deficiencies. Rather, Applicants assert the Examiner is 'picking and choosing' features from various pieces of art and combining them to arrive at the claimed invention, which amounts to inappropriate hindsight reconstruction. Applicants further assert that because no deficiencies were noted by Badylak et al nor Penn, particularly problems that encapsulation would solve, it is inappropriate to maintain the obviousness rejection.

Applicants arguments have been fully considered, but are not found persuasive.

With regards to the appropriateness of the combination of teachings of Badylak et al (2003), Badylak et al (1999) and Penn (2004), the Examiner's response from above is incorporated herein.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, it has been established that each of the features of the claimed invention were well known in the art at the time the invention was made, and the Examiner has articulated a rationale supporting their combination, specifically: "any transplanted cell may be subject to immune rejection, thus, in order to protect the genetically engineered cells to ensure that they survive to express the VEGF, it is submitted that it would have been *prima facie* obvious to one having ordinary skill in the art to encapsulate the genetically engineered first cell population, and provide this encapsulated first cell population along with the cell-based tissue construct of Badylak et al to the target tissue site. Stewart et al disclose various microcapsules, including alginate-poly(L-lysine) microcapsules (please note microcapsules and microspheres are synonymous in this context) (See Stewart et al, ¶0010)." Though Applicants find this

conclusion to be insufficient to support obviousness, it is maintained that an effort to protect against immunorejection is sufficient motivation to encapsulate cells.

5. Applicants have traversed the rejection of claim 23, 25, 26 and 28 under 35 USC 103(a) over Naughton et al (2003), in view of Penn (2004) on the grounds that Naughton et al fail to teach co administration of two separate cell populations with different functions. Rather Applicants assert Naughton et al intends for the stromal tissue construct to comprise fibroblasts *or* other stromal cells as alternatives to fibroblasts, citing ¶0039 of Naughton et al. Thus, Applicants assert Naughton et al teaches away from the instant invention. Applicant asserts that Penn fails to remedy the deficiencies of Naughton et al and that there is no 'nexus' provided between the references.

Applicants' response has been fully considered, but is not found persuasive.

In response to Applicants' first argument, that Naughton et al does not teach two separate populations of stromal cells, but rather only teaches the disclosed cell types as alternatives to one another, It is believed the paragraph which Applicants are citing is actually ¶0038, and the first sentence of the paragraph (which Applicants omitted), reads "In addition to fibroblasts, other cells may be added to form the three-dimensional stromal tissue..." (emphasis added). The other cells may be "inoculated onto the three-dimensional framework along with, or instead of, fibroblasts..." (*id*). Therefore, while Naughton et al teach that the other cell types may be an alternative to fibroblast, there is equal suggestion that the other cell types may be in *addition to* fibroblasts, as relied upon for the rejection of record. Thus, Naughton et al does not teach away from inclusion of a secondary cell type.

In response to Applicants' argument that there is no established 'nexus' between the primary reference Naughton et al (2003) and Penn et al (2004), it is respectfully submitted that both references are directed to cell-based implants for tissue engineering, and specifically for promoting vascularization at the implant site. Naughton et al specifically disclose an embodiment wherein a stromal tissue graft is

implanted adjacent to ischemic myocardium (See Naughton et al, ¶0055-0058). Penn et al provides an embodiment for improving vascularization of ischemic myocardium by injection of transiently transfected cells (See, e.g. Penn et al ¶0009 & 0067-0072). Rationale for combining the cited references has been clearly set forth: "Because Naughton et al disclose an embodiment wherein the stromal tissue construct of is implanted adjacent to ischemic myocardium for the purpose of restoring or improving cardiac function by inducing angiogenesis at the ischemic region (See Naughton et al, ¶0055-0058), one having ordinary skill in the art would have been motivated to apply the technique of Penn et al, involving transiently transfecting cells to transiently express VEGF to the cells contained within the stromal construct of Naughton et al for the purpose of reducing the likelihood of hemangioma formation while still stimulating angiogenesis. One would have had a reasonable expectation of successfully transiently transfecting the additional cell population (the endothelial and/or cardiac muscle cells) of Naughton et al by the techniques of Penn et al based on the success shown by and detailed protocols provided by Penn et al in their disclosure." Therefore, the rejection is maintained as proper.

6. Applicants have traversed the rejection of claims 23, 25, 26, 28, 29, 40 and 41 under 35 USC 103(a) as being unpatentable over Naughton et al (2004) in view of Penn et al (2004) on the grounds that the combination of teachings of Naughton et al (2004) in view of Penn et al (2004) are inappropriate for the reasons set forth above, and that the Examiner has relied on inappropriate hindsight reconstruction.

Applicants' arguments have been fully considered, but are not found persuasive.

Applicants are respectfully directed to the discussion presented above for the appropriateness of the combination of Naughton et al (2004) in view of Penn et al (2004).

7. Applicants have traversed the rejection of claims 23-26 and 28 under 35 USC 103(a) over Naughton et al (2004) in view of Penn et al (2004), and further in view of Atala et al on the grounds that

the combination of teachings of Naughton et al (2004) in view of Penn et al (2004) is inappropriate for the reasons set forth above, and that Atala et al fails to remedy the deficiency.

Applicants' arguments have been fully considered, but are not found persuasive.

Applicants are respectfully directed to the discussion presented above for the appropriateness of the combination of Naughton et al (2004) in view of Penn et al (2004).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, it has been established that each of the features of the claimed invention were well known in the art at the time the invention was made, and the Examiner has articulated a rationale supporting their combination, specifically Naughton et al and Atala et al each individually teach matrix materials capable of supporting cell attachment and growth in more than one layer, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one matrix material (the decellularized tissue of Atala) for the other (the disclosed materials of Naughton et al) for the predictable result of successfully supporting growth of cells thereupon for formation of an engineered tissue construct which may subsequently be implanted at a target site. Substitution of one element for another known in the field is considered to be obvious, absent a showing that the result of the substitution yields more than predictable results. See *KSR International Co. v Teleflex Inc* 82 USPQ2d 1385 (US 2007) at page 1395."

8. Finally, Applicants have traversed the rejection of claims 23, 25, 26, 28, 33 and 36-37 as being unpatentable under 35 USC 103(a) over Naughton et al, Penn et al, and Stewart et al on the grounds that

the Examiner has failed to provide any reason why one of ordinary skill in the art would combine the elements in the same way as the claimed invention or why one would disregard the teachings of Naughton et al to the use of one population of cells.

Applicants' arguments have been fully considered, but remain unpersuasive.

As discussed above Naughton et al does appropriately teach use of multiple cell types. Furthermore, it has been clearly articulated that one having ordinary skill in the art would have been motivated to encapsulate at least one cell population of Naughton et al for the purpose of providing enhanced immune protection fro the cells, as taught by Stewart et al. The reasoning has been clearly articulated, and the rejection therefore stands as proper.